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Complete List of Authors:	Knutson, K; Northwestern University Feinberg School of Medicine, Department of Neurology; Northwestern University Feinberg School of Medicine, Department of Preventive Medicine Pershing, Mandy; Northwestern University Feinberg School of Medicine, Department of Preventive Medicine Abbott, Sabra; Northwestern University Feinberg School of Medicine, Department of Neurology Alexandria, Shaina J.; Northwestern University Feinberg School of Medicine, Department of Preventive Medicine Chiluka, Sindhu; Northwestern University Feinberg School of Medicine, Department of Preventive Medicine Chirinos, Diana; Northwestern University Feinberg School of Medicine, Department of Preventive Medicine Giachello, Aida; Northwestern University Feinberg School of Medicine, Department of Preventive Medicine Gupta, Niket; Northwestern University Feinberg School of Medicine Harrington, Katharine; Northwestern University Feinberg School of Medicine, Department of Preventive Medicine Rittner, Sarah S.; SASU Project Management Sorond, Farzaneh; Northwestern University Feinberg School of Medicine, Department of Neurology Wong, Mandy; Northwestern University Feinberg School of Medicine, Department of Preventive Medicine Vu, Thanh-Huyen ; Northwestern University Feinberg School of Medicine, Department of Preventive Medicine Zee, Phyllis C.; Northwestern University Feinberg School of Medicine, Department of Neurology Carnethon, Mercedes; Northwestern University Feinberg School of Medicine, Department of Preventive Medicine
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A Protocol for an Epidemiologic Study of Disparities in Sleep and Cognition in Older Adults (DISCO)

Authors:

Kristen L. Knutson[1,2], Mandy L. Pershing[2], Sabra Abbott[1], Shaina J. Alexandria[2], Sindhu Chiluka[2], Diana Chirinos[2], Aida Giachello[2], Niket Gupta [3], Katharine Harrington[2], Sarah S. Rittner[4], Farzaneh Sorond[1], Mandy Wong[2], Thanh-Huyen T. Vu[2], Phyllis Zee[1], Mercedes R. Carnethon[1,5]

Author affiliations:

1. Department of Neurology, Northwestern University Feinberg School of Medicine
2. Department of Preventive Medicine, Northwestern University Feinberg School of Medicine
3. Northwestern University Feinberg School of Medicine
4. SASU Project Management
5. Department of Medicine, Division of Pulmonary and Critical Care, Northwestern University Feinberg School of Medicine

Author Contributions

All authors have contributed to the design of this protocol. AG, DC, FS, KH, KLK, MRC, PZ, SA, and TTV initiated and conceptually designed the project. SC is acquiring data. This protocol was drafted by KH, KLK, MLP, MRC, MW, SC, SJA, and SSR, and was refined for critically important content by DC, SSR, and TTV. Statistical advice was provided by MW and SJA. KLK and MRC obtained funding for the study. All authors approved the final manuscript.

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Patient and public involvement

Patients and/or the public were involved in the design, conduct, and dissemination plans of this research. Refer to the Methods section for further details.

Conflicts of Interest

There are no conflicts of interest to report.

Contact Information:

Kristen L. Knutson, PhD

Associate Professor

Center for Sleep and Circadian Medicine

Department of Neurology

Northwestern University Feinberg School of Medicine

710 N Lakeshore Drive, Room 1003

Chicago, IL 60611

Tel: 312-503-1526

Email: kristen.knutson@northwestern.edu

ORCID: https://orcid.org/0000-0002-2751-6168

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ARTICLE SUMMARY

Abstract

Introduction: Cognitive dysfunction, a leading cause of mortality and morbidity in the US and globally, has been shown to disproportionately affect the socioeconomically disadvantaged and those who identify as Black or Hispanic/Latinx. Poor sleep is strongly associated with the development of vascular and metabolic diseases, which correlate with cognitive dysfunction. Therefore, sleep may contribute to observed disparities in cognitive disorders. The Epidemiologic Study of Disparities in Sleep and Cognition in Older Adults (DISCO) is a longitudinal, observational cohort study that focuses on gathering data to better understand racial/ethnic sleep disparities and illuminate the relationship among sleep, race, and ethnicity and changes in cognitive function. This investigation may help inform targeted interventions to minimize disparities in cognitive health among aging adults.

Methods and analysis: The DISCO study will examine up to 495 individuals aged 55 and older at two time points over 24 months. An equal number of Black, White, and Hispanic/Latinx individuals will be recruited using methods aimed for adults traditionally underrepresented in research. Study procedures at each time point will include cognitive tests, gait speed measurement, wrist actigraphy, a type 2 home polysomnography and a clinical exam. Participants will also complete self-identified assessments and questionnaires on cognitive ability, sleep, medication use, quality of life, sociodemographic characteristics, diet, substance use, and psychological and social health.

Ethics and Dissemination: This study was approved by the Northwestern University Feinberg School of Medicine Institutional Review Board. De-identified datasets will be shared via the BioLINCC repository following the completion of the project. Biospecimen samples from the study that are not being analyzed can be made available to qualified investigators upon review and approval by study investigators. Requests that do not lead to participant burden or that conflict with the primary aims of the study will be reviewed by the study investigators.

Strengths and Limitations

- Strength: Multiple race and ethnic groups are examined in a single study with identical instrumentation and methodology applied across groups.
- Strength: This is a longitudinal follow up study to determine temporality.
- Strength: Gold standard instruments illustrate objective determination of habitual sleep and sleep architecture.
- Limitation: Sample is not generalizable for the population since random sampling is not used.

Keywords

sleep medicine, dementia, epidemiology, health equity, public health

INTRODUCTION AND RATIONALE

Dementia, including Alzheimer's disease, is a severe manifestation of cognitive dysfunction and among the top 10 causes of death in the US and globally.[1] Morbidity from less severe cognitive dysfunction is equally notable, since cognitive dysfunction alone, although not terminal in most cases, still requires progressive social and medical support. Cognitive dysfunction affects some persons more than others, and these groups often share social and demographic characteristics. Persons with fewer socioeconomic resources, less education, or those who identify as Black or Hispanic/Latinx disproportionately experience higher rates of acute and chronic illnesses.[2] Reasons for disparities among those communities are hypothesized to arise from disparities in several underlying clinical conditions that are known to predispose cognitive dysfunction, including sleep disorders, metabolic disorders, and vascular disorders such as coronary heart disease, stroke, hypertension and diabetes.[3] Given the irreversibility of cognitive dysfunction, identifying and addressing these modifiable factors that are associated with cognitive decline could reduce disparities in cognitive dysfunction.[4]

Cardiovascular and metabolic disorders have been associated with insufficient habitual sleep, poor quality sleep, and presence of sleep disorders in longitudinal observational studies.[5-7] Experimental human studies that restricted or impaired sleep demonstrated a causal relationship of short or disturbed sleep with changes in metabolism that predispose to obesity and other metabolic disorders.[8] Similarly, interventions to improve sleep disorders (such as obstructive sleep apnea or insomnia) or to increase sleep duration show significant benefits for blood pressure control, glucose metabolism, and weight loss.[9-12] Further, insufficient sleep and sleep disorders, such as obstructive sleep apnea, have been associated with cognitive dysfunction; therefore, insufficient or poor quality sleep may be a modifiable risk factor for cognitive decline, which may act partly through impairments of cardio-metabolic function.[13-16] There are also racial and ethnic disparities in sleep that parallel disparities in cognitive function, cardiovascular disease, and metabolic disorders: non-Hispanic Black and Hispanic/Latinx adults are more likely to be short sleepers, long sleepers, have poorer sleep quality, and a higher prevalence of sleep disorders (such as obstructive sleep apnea), as compared to non-Hispanic White adults.[17-20] Studies using polysomnography (PSG) have observed worse sleep architecture, such as less deep sleep and more awakenings, among Black adults compared to White adults.[21-23] Furthermore, these disparities exist among older adults: the Multi-Ethnic Study of Atherosclerosis Sleep Cohort (MESA) examined sleep characteristics in men and women aged 54-93 years and found that compared to White older adults, Black older adults were more likely to have sleep apnea syndrome (AHI ≥ 5 plus sleepiness), shorter sleep durations, and poorer sleep quality and that Hispanic/Latinx older adults were more likely to have sleep disordered breathing and shorter sleep.[24] Therefore, non-Hispanic Black and Hispanic/Latinx older adults are more likely to have inadequate sleep and one of our aims was to identify some determinants of these sleep disparities.

In response to gaps in the literature on both the determinants of sleep disparities and the role that sleep has on disparities in cognitive dysfunction, we formed the Disparities in Sleep and Cognition in Older Adults (DISCO) study.

Specific Aims

The primary objectives of the DISCO study are twofold. The first is to examine numerous social, behavioral, and health-related characteristics as possible explanations for racial and ethnic sleep health

disparities. The second is to determine whether disparities in sleep health by race and ethnicity are significant contributors to disparities in the rate of cognitive decline over the course of 2 years.

The scientific premise of our study is based on the following observations by our team and others as described above: 1. Persons who identify as non-White and/or Hispanic/Latinx and who have less education (the socioeconomically disadvantaged) have less favorable sleep and circadian rhythm characteristics than their counterparts; 2. Less favorable sleep and circadian rhythm characteristics are associated with cognitive dysfunction; and, 3. Cognitive dysfunction is more common among socioeconomically disadvantaged persons. The study has 2 primary aims:

1. Define the contribution of psychological well-being, social well-being, and clinical characteristics to sleep disparities.

We will test the hypotheses that sleep disparities are partially explained by lower psychological well-being, greater stress, lower self- efficacy, and lower social support among non-White adults; and by a higher burden of prevalent comorbidities, such as heart failure or diabetes among non-White adults.

2. Determine whether sleep disorders mediate racial or ethnic differences in the change in cognitive function over 24 months.

We hypothesize that inadequate sleep will be associated with greater cognitive decline and will partially mediate the racial and ethnic differences in change in cognitive function over 2 years. We will additionally explore mechanistic pathways to account for these associations, including the presence of cerebral small vessel dysfunction and insulin resistance.

METHODS

Study design

The DISCO study is a longitudinal observational cohort study that will examine an equal number of non-Hispanic Black, non-Hispanic White, and Hispanic/Latinx adults of any race aged 55 years and older. Participants will be examined at baseline and again approximately 24 months later. To include 450 individuals at each time point, we are enrolling approximately 495 participants at baseline to account for 10% missing data. Women and men will be enrolled at proportions that reflect older age distribution according to the 2019 US Census (54% and 46%, respectively).

Study setting

This is a single-site study in the metropolitan Chicago area and surrounding suburbs, and nearby northwest Indiana and southern Wisconsin. Participants are locally recruited from these areas since they must come into the study clinic for data collection, located in downtown Chicago. Car travel to and from the clinic is arranged by study staff, if needed.

Recruitment methods

Participants are recruited through a combination of strategies including random sampling of commercially available telephone listings, community engagement strategies, institutional electronic health records, advertisements on social media and in publicly available locations, and word of mouth

(i.e., snowball sampling). Our sampling approaches using commercially available sampling and the electronic health record sampling are similar: first, our staff mails or emails a letter to potential participants that includes an explanation of the study and an invitation to contact study staff either by telephone, email, or visiting our study website to learn more and assess eligibility. Staff follow the letters by contacting participants via phone to explain the study, invite participation, screen for eligibility, and obtain consent.

Advertisements for our study are placed in newspapers, at community sites (e.g., public libraries, cafes, senior living facilities), on public transportation, and on Facebook. The advertisements include a link to our study website and staff phone numbers so that individuals can request more information about the study and complete preliminary screening questions to determine their eligibility.

Targeted recruitment strategies

We use two additional strategies to address the challenges of recruiting individuals who are traditionally underrepresented in research studies. One such strategy is "snowball sampling," whereby staff asks participants who complete the study to refer us to people outside of their household who are socio-demographically similar (based on race, ethnicity, and age) who might also be interested in participating. Study staff ask the participants to share our study flyer and website with these friends and family.

Patient and public involvement

Our second strategy to reach adults who are traditionally underrepresented in research is using community engagement activities.[25] These activities call for the active involvement of community leaders, organizations, and other sectors or stakeholders (such as departments of health) working with academic institutions in the development, implementation, and evaluation of research priorities and activities. Some of the activities include: the engagement of Chicago-area community-based grassroots and health and human services organizations, local and state government representatives, professional organizations, and other sectors that are not traditionally involved in research.

DISCO convenes a Community Advisory Board (CAB) every six-months to provide recommendations on project activities, suggest community engagement opportunities, discuss strategies for recruitment and retention, build relationships with community groups, and inform our team about community events. Most CAB members were identified from organizations that serve Black and Hispanic/Latinx communities in the city of Chicago. While a core group of 3-4 CAB members remain engaged in the study since its inception, the CAB also includes some older adults who enrolled in the DISCO study and joined the CAB after their study participation. When study results are available, the CAB will advise on strategies to disseminate the findings back to the community who contributed to the research.

Impact of the COVID-19 Pandemic on Recruitment

The COVID-19 pandemic greatly impacted study recruitment due to the vulnerability of older adults to severe outcomes from SARS-CoV-2.[26] The research clinic was also closed from March 16 through June 1, 2020. With the CAB's recommendations and the hiring of a Community Engagement Consultant, DISCO pivoted to virtual-only engagement strategies and recruitment activities from March 2020 – June 2022. We provided virtual educational sessions on Sleep and Aging, Research and Aging, Sleep and Aging in Hispanic/Latinx Communities, and Sleep and Aging in Black & African American Communities. We

bolstered marketing via Facebook and television, as well as print advertisements in neighborhood and citywide English and Spanish language newspapers. We broadened partnerships for in-person outdoor events once it was deemed safe enough during the summer of 2022. Changes were also made to the study protocol and in the clinical research clinic to maximize public safety for the staff and public.

Eligibility criteria

Potential participants who express interest are contacted by study staff to determine eligibility. See Table 1 for inclusion and exclusion criteria.

Participants who are deemed eligible are given the Montreal Cognitive Assessment (MOCA) test either in-person or via the telephone.[27] To administer over the phone (a process that was approved following the pandemic to avoid unnecessary in-person contact), the BLIND MOCA is used, which is a version designed for people with visual impairment. Both versions contain cognitive domains such as attention, concentration, memory, language, conceptual thinking, calculation, and orientation. A pass score on the original MOCA is 26/30, and a pass score on the BLIND MOCA is 18/22. Participants who indicate that their preferred language is Spanish are administered the validated Spanish-language version of the MOCA. If they pass, study staff solicit verbal consent over the telephone and obtain a signed consent using REDCap.

DATA COLLECTION

Examination Structure

The baseline assessment is comprised of three steps. Step 1 takes place prior to the clinical examination when participants complete questionnaires. We offer the first set of questionnaires (in Spanish or English) electronically via REDCap, by mailing a copy to the participant's home, or they may alternatively be completed in the clinic with staff. Table 2 shows the survey instruments and the domains they collect. Once those are complete and received, study staff contact participants to schedule their clinical examination at our research clinic. Step 2 invites participants to our research clinic to undergo a fasting blood draw, anthropometric measures, blood pressure assessment, six-minute walk test, NIH Toolbox, and to receive the sleep equipment that they will wear in their homes. During Step 3, participants complete additional cognitive function testing, gait analysis, and measurement of cerebral blood flow. Participants have the option of splitting their baseline examination into two separate visits by completing Step 2 and then bringing their sleep equipment back for Step 3 eight days later or completing the final two steps in a single visit. The latter option was introduced following COVID-19 to reduce time spent in the clinic. Participants repeat these three steps a minimum of 24 months after their baseline assessment. All data is stored electronically via REDCap and on a secure, encrypted, password-protected server.

Assessment of Cognitive Function

A primary outcome in the study is cognitive function as determined using the *NIH Toolbox cognition battery*.[28,29] Participants whose preferred language is Spanish are administered the NIH Toolbox Spanish translation. DISCO participants complete the tests that assess attention,[30] executive and memory domains,[31] and episodic memory[32,33] because of the overlap between Alzheimer's Disease and vascular cognitive impairment (cerebral small vessel disease) in this age group.[34]

A second measure of cognitive abilities is determined using the PROMIS Applied Cognition Abilities Instrument, which is a 16-item measure evaluating self-impressions of cognitive function in the previous seven days in areas such as mental acuity, concentration, and memory.[35]

Sleep Assessment

We are using several methods to assess sleep health in the DISCO study that are consistent with gold-standard measures for in-home unattended assessments in observational population studies.

Wrist Actigraphy

Sleep-wake activity is measured over 7-8 days using wrist activity monitors (Actiwatch Spectrum Plus or Pro ™, Philips Respironics). Wrist actigraphy has been validated against polysomnography (the gold standard of sleep measurements), demonstrating a high correlation for sleep duration among both people with insomnia (r=.82) and in healthy people (*r* = 0.97) with a discrepancy ranging from 12 to 25 minutes.[36] This method is thought to be a more accurate representation of habitual sleep patterns than polysomnography because it is less disruptive to sleep, can be carried out in the home, and is usually averaged over multiple days. Participants also complete a simple sleep diary and are asked to push the event marker button each time they try to go to sleep and when they wake up.

The actigraphy recordings are scored by a trained technician following specific study guidelines regarding the use of event markers, sleep diary and the activity and light data from the device. We document which method was used to determine the start and end of all rest intervals. All scored recordings are reviewed by PI and Sleep Specialist Dr. Knutson. We use the validated algorithms included in the Actiwatch ™ software analysis system (Actiware) to calculate several measures for each rest interval. The primary actigraphic estimates of habitual sleep include: 1. sleep duration; 2. sleep percentage (%, the sleep period actually spent sleeping; 3. sleep fragmentation (an index of restlessness). We also are calculating rest-activity rhythms and sleep regularity indices using previously published methods.[37,38]

Type 2 Polysomnography

Attended, in-laboratory, full-polysomnography recordings are the gold standard method to assess sleep architecture (i.e., sleep stages) and respiratory events; however, this method is burdensome on the subject. Thus, we have selected an easy-to-use EEG monitor that can be self-applied and worn at home. We are using the Sleep Profiler ™ system (Advanced Brain Monitoring, Carlsbad, CA) to assess sleep stages, spectral power, and respiratory events. The system has configurable acquisition of up to six channels of electro-physiological signals to acquire electroencephalography (EEG), electromyography (EMG), electrooculography (EOG), and electrocardiography (ECG) signals. The device also includes respiratory measures via airflow adapter, cannula, wireless WristOx, Thorax and Abdomen Piezo belts. Several validation studies have been performed comparing the Sleep Profiler to polysomnography and demonstrated strong agreement between these methods.[39,40] In addition, analysis of two nights of recording demonstrated stability in the measures of the sleep stages, indicating the Sleep Profiler provides valid measures of sleep stages with a single night.[41]

Participants are asked to wear the device for one night and are given detailed instructions and demonstrations, along with both videos and written instructions. The system firmware monitors signal quality to ensure that the sensors are properly applied and that high-quality signals are being acquired.

Impedance checking is automatically initiated when acquisition begins. Voice messages are delivered to the patient if the impedances are too high or the sensors have become detached. We disable any voice messaging during sleep, however, because we do not want to impair the sleep of the participants. The acquired signals are saved in a universal data format (European Data Format – EDF) that can be analyzed with third party software, if needed. For our primary analyses, we are using the Sleep Profiler cloud that includes automatic scoring and staging. The pulse rate is analyzed to detect autonomic activation. Head movement is used to assist in detecting sleep/wake and to identify periods with gross movement which result in artifact or indicate behavioral arousals. The software provides visual presentation of the recordings and the ability to rescore by a technician. All recordings are reviewed by a trained technician who modifies the analysis if needed.

The Sleep Profiler System provides the following measures: minutes and percentage of stages of rapid eye movement (REM) sleep, non-REM sleep (N1, N2, N3), sleep latency, wake-after-sleep-onset (WASO), sleep efficiency, arousals, pulse rate, and average power spectra, including delta (or slow-wave activity). The software also detects apneas and hypopneas based on either 3% or 4% desaturation. We are using the American Academy of Sleep Medicine definition of hypopnea when there is a ≥ 3% oxygen desaturation from pre-event baseline and/or the event is associated with an arousal.[42] We then calculate the apnea-hypopnea index (AHI; events/hour).

Sleep Questionnaires

Participants complete several questionnaires to assess subjective sleep quality and chronotype preferences.[43] The following validated instruments are collected at both time points: the Pittsburgh Sleep Quality Index,[44] Insomnia Severity Index,[45] Morningness-Eveningness Questionnaire,[46] Epworth Sleepiness Scale,[47] and the Brief Index of Sleep Control.[48] See Table 2 for a description of each instrument.

Other Measurements

Table 2 lists the remaining domains that are assessed in the study. We selected these domains with the goal of capturing the multidimensional factors that could influence sleep or cognitive function. We assessed a broad set of social determinants of health that we know underlie disparities in health behaviors and disease outcomes by race and ethnicity. All questionnaires that did not have Spanish language translations available were translated by our study team or professional translation company and reviewed by two additional Spanish-speaking co-investigators.

Sociodemographic characteristics including race, ethnicity, age, and educational level were determined based on self-report from the participants. Wherever possible, validated questionnaires were used to assess covariates that we hypothesized were associated with sleep, cognitive function, or both.

Participants are also asked to walk across a 25-ft mat (ZenoMat, Protokinetics, PA) and their walking speed is measured during two trials in order to measure gait speed, which has been strongly associated with blood pressure, cardiovascular disease and stroke.[49-52]

DATA MANAGEMENT

Sample size and power calculation

Analyses in both aims will include the entire proposed sample of 495 recruited participants. Power to detect clinically meaningful effect sizes were calculated conservatively assuming 9% (n=450) and 18% (n=405) of participants would have missing data for primary analyses or would be lost to attrition. A study that examined sleep quality, including percentage of wake after sleep onset (WASO),[53] found that sleep after days with lower subjective stress had a lower percentage of WASO than sleep after days with higher stress (mean WASO% = 12.2% vs. 16.4%, SD = 12.1% vs. 14.9%). We have 91% power to detect these differences with the proposed sample of 450 participants and 87% power to detect this difference assuming 10% attrition (n=405) in Aim 1 analyses. For power analyses using the Structural Equation Modeling (SEM) approach in Aim 2, we calculate the power to detect both unacceptable model-fit using Root Mean Square Error of Approximation (RMSEA) and effect sizes. With a sample size of n=450, we achieve 92% power to detect an RMSEA of 0.1 (unacceptable model fit) against the null hypothesis of RMSEA = 0.5 (good model fit). With a sample size of n=450 participants and using RMSEA = 0.05 under the null hypothesis of a good model fit and RMSEA = 0.1 under the alternative hypothesis of unacceptable model fit, we can achieve a power of 92% by observing 5 variables of interest. Assuming 10% are lost to follow-up after baseline, with the sample size of n=405 we can achieve a power of 89%.[54] With the proposed sample size, we can achieve an effect size of 0.2 (small-moderate effect size) with 5 observed variables and 5 latent variables.[55,56] Furthermore, with n=405, we achieve 87% power to detect an odds ratio of 3:1 in cognitive decline for the group with adequate sleep compared to the group with inadequate sleep.

Quality Control and Quality Assurance

Study data are collected using electronic methods that constrain response ranges to plausible ranges. Participants either enter responses directly into the REDCap system or data are entered by study staff members who interviewed study participants. The analytical team meets monthly to review data regarding data completeness, data quality and additional data topics as needed. This process will ensure proper data management, scoring of questionnaires and completion of study procedures in a timely manner.

Data analysis plan

General considerations: In all analyses, distributional characteristics of each measure and residual diagnostics will be used to assess modeling assumptions. As needed, transformations, nonparametric methods, and/or inclusion of higher-order (quadratic, cubic, interaction, etc.) terms may be considered in analytic models. Statistical estimates (e.g., regression coefficients) will be reported with accompanying 95% confidence intervals and p-values as applicable. We will use type I error rate of 0.05 to assess statistical significance, while also qualitatively determining if the effect magnitude is clinically meaningful.

Missing data: The multilevel models planned for analysis of longitudinal data are generally robust for unbalanced data across study time points. Nonetheless, multiple imputation with chained equations will then be used to examine the sensitivity of findings to missing data.[57] For non-ignorable missing data, we will conduct sensitivity analyses using non-ignorable pattern-mixture and selection models to investigate the robustness of our conclusions across the different models for missing data.

Analyses for Aim 1. To evaluate the contribution of psychosocial characteristics to sleep disparities, we will examine the cross-sectional associations between measured psychosocial variables and objective

and subjective measures of sleep. We will fit regularized regression models (e.g., LASSO, elastic net) for each sleep outcome (e.g., WASO, PSQI) that include interaction terms between race and psychosocial characteristics to assess effect modification by race.[58] These models will be adjusted for sociodemographic characteristics and comorbidities measured at the baseline visit. The final models will identify the psychosocial variables that best explain each sleep outcome. Additional analyses will stratify by OSA (i.e., AHI < or >= 15) and by sex.

Analyses for Aim 2. We will assess whether inadequate sleep is associated with greater cognitive decline over 24 months via mixed-effects models for change in continuously determined cognitive function score, with a random intercept for participant to account for the correlation that arises from measuring multiple time points from an individual.[59] The mixed-effects models will be adjusted for time-invariant (e.g., sex) and time-varying (e.g., body mass index, comorbid disease) covariates. Results from this analysis will inform whether baseline sleep measurements or change in sleep measurements will be used in subsequent analyses. To assess whether inadequate sleep mediates racial/ethnic differences in change in cognitive function over 24 months, we will use two approaches to mediation analysis: the Baron and Kenny mediation method and Vanderweele's causal mediation method, which allows for interactions between the independent and mediator variable.[60-62] Furthermore, we will test for interactions between the sleep variables and race/ethnicity to determine if different aspects of sleep vary by race. We will use the same analytic approach to test to what extent cerebral vascular blood flow or insulin resistance mediate the association between sleep metrics and cognitive function.

ETHICS and DISSEMINATION

The DISCO study is approved by the Northwestern University Feinberg School of Medicine Institutional Review Board (IRB). As stated above, informed consent is obtained in writing from participants and stored in Study Tracker. All data will be de-identified before sharing the results, posing no risk to participant confidentiality.

De-identified datasets will be shared via the BioLINCC repository following the completion of the study. In addition to the ongoing processing of biospecimens during the study, study investigators are banking serum, plasma and buffy coat. Samples that are not being analyzed can be made available to qualified investigators with a materials transfer agreement and/or data use agreement as applicable. The study investigators will review and consider all requests that do not lead to participant burden nor conflict with the primary aims of the study.

Table 1. Inclusion and exclusion criteria

Inclusion	Exclusion
At least 55 years of age at the time of enrollment	Currently undergoing treatment for cancer (other than non-melanoma skin cancer)
Non-Hispanic Black, non-Hispanic White, or Hispanic/Latinx of any race	Clinical vascular event including myocardial infarction, stroke, transient ischemic attack, or procedure to treat those conditions within the previous 6 months
Able to read and understand either English or Spanish	Chronic heart failure classes II-IV
	Diagnosis of dementia (including Alzheimer's disease)
	Living in a group home, assisted living or other institution
	Overnight shift work or swing shift work that spans midnight (12:00am)
	Severe vision or hearing deficits that would interfere with testing
	Regular use of medications in the following classes: hypnotics, psychoactive medications with anti-cholinergic and antihistaminic effects, or opioids
	Severe chronic obstructive pulmonary disease
	Inability to move both arms
	Prior diagnosis of severe neurological disorders
	Montreal cognitive assessment (MOCA) score < 23 if administered the in-person version, or <18 if administered the over-the-phone version
	Inability to give consent

Table 2. List of survey instruments used in this study

Instrument	Description
Cognitive Domain	
MOCA[63]	Assessment tool for the early detection of mild cognitive impairment. Assesses short-term memory, visuospatial abilities, executive function, attention, concentration and working memory, language and orientation to time and place.
PROMIS Applied Cognition Abilities[33]	16-item measure assessing self-impressions of cognitive function in the past 7 days.

Sleep Domain	
Pittsburgh Sleep Quality Index[44]	19-item instrument to estimate subjective sleep quality. Scores range from 0 to 21; higher scores indicate worse sleep quality.
Insomnia Severity Index[45]	7-item instrument that assesses severity of insomnia. Higher scores indicate worse insomnia symptoms.
Morningness-Eveningness[46]	19-item instrument that assesses preferred "chronotype", or morningness vs eveningness. Higher scores indicate greater morningness.
Epworth Sleepiness Scale[47]	8-item questionnaire to estimate daytime sleepiness. Higher scores indicate greater sleepiness.
Brief Index of Sleep Control[48]	4-item instrument designed to quantify the degree to which someone has control over their sleep. Higher scores indicate greater control.
Health Domain	
Medication Use	This form collects details on prescription medication used in the past 4 weeks or over-the-counter medication used in the past 2 weeks.
Medical History	23-item questionnaire that records information about individuals' medical history. High scores indicate better health.
SF-36 Questionnaire[64]	36-item measure assessing health-related quality of life. Scores are summarized in a Physical Component Summary (PCS) and Mental Component Summary (MCS). Higher scores indicate better health status.
KC Cardiomyopathy Questionnaire[65]	23-Item measure examining heart failure symptoms, physical limitations and quality of life. Lower scores represent more severe symptoms/limitations.
PROMIS Global Health[66]	10-item scale that assesses physical, mental, and social aspects of health. Higher scores indicate better health.
Time Use Questionnaire	7-item scale that assesses the frequency and duration of activities.
COVID-19 Questionnaire	15-item questionnaire that related to exposure to COVID-19.
Sociodemographic Domain	
Sociodemographic Information Questionnaire	38 items are collected to assess sociodemographic characteristics such as age, gender, ethnicity, education level, income, access to healthcare, perceived social standing etc.
Lifestyle Behavior Domain	
GPAQ[67]	13-item scale examining several components of physical activity including intensity, duration and frequency.
Tobacco History	11- item questionnaire that determines when an individual began smoking and their current smoking habits.
ASA 24-Hour Dietary Recall[68]	Automated self-administered 24-hour dietary assessment tool web-based tool.
Substance Use	12-item questionnaire that determines the use of alcohol and marijuana.
Psychosocial Domain	

STRAIN[69]	The Stress and Adversity Inventory (STRAIN) is a secure, online stress assessment system that measures individuals' lifetime exposure to different types of acute and chronic stress that can affect mental and physical health. The system is intended to combine the reliability and sophistication of an interview-based measure of stress with the simplicity of a self-report instrument. To accomplish this goal, the STRAIN enquires about 75 different types of stressors (Adolescent STRAIN) or 55 different types of stressors (Adult STRAIN) that cover all major life domains (e.g., health, intimate relationships, friendships, children, education, work, finances, housing, living conditions, crime, etc.) and several social-psychological characteristics (e.g., interpersonal loss, physical danger, role change, entrapment, etc.).
PROMIS Social Isolation - Short Form 4a[70]	6-item scale examining perceived social isolation. Higher scores indicate higher perceived isolation.
Quick Inventory of Depressive Symptomatology QIDS-SR16[71]	16-item scale examining endorsement of depressive symptoms. Higher scores indicate higher symptoms.
Perceived Stress Scale[72]	10-item scale assessing the degree to which situation in participant's life are appraised as stressful. Higher scores indicate higher levels of stress.
UCLA Loneliness Questionnaire[73]	8-item scale assessing perceived isolation from others. Higher scores indicate higher perceived loneliness.
GAD Anxiety[74]	7-item questionnaire assessing self-reported anxiety symptoms in the past two weeks. Higher scores indicate higher anxiety symptoms.
Brief Resilience Scale[75]	6-item questionnaire used to assess the ability to bounce back. High score indicated high resilience,
Bereavement	1-item examining whether participants have lost a spouse/partner or loved one in the past 6-months.
USDA Food insecurity[76]	5- item questionnaire used to measure household food security and food insecurity. High score indicated extremely low food security.
Social Support[77]	8- item questionnaire indicated the number of people available for support and satisfaction of support.

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Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a

Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	n/a
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1-2
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	1
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support			
Sources	#5a	Indicate sources of financial or other support for the review	1
Sponsor	#5b	Provide name for the review funder and / or sponsor	1
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	1
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is	4

		already known	
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	12
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	5
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Study records - data collection	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any	10

process		processes for obtaining and confirming data from investigators	
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	10
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	10
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within	3

		studies)	
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	10

BMJ Open

Study Protocol for a Longitudinal Observational Study of Disparities in Sleep and Cognition in Older Adults: The DISCO Study

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Study Protocol for a Longitudinal Observational Study of Disparities in Sleep and Cognition in Older Adults: The DISCO Study

Authors:

Kristen L. Knutson[1,2], Mandy L. Pershing[2], Sabra Abbott[1], Shaina J. Alexandria[2], Sindhu Chiluka[2], Diana Chirinos[2], Aida Giachello[2], Niket Gupta [3], Katharine Harrington[2], Sarah S. Rittner[4], Farzaneh Sorond[1], Mandy Wong[2], Thanh-Huyen T. Vu[2], Phyllis Zee[1], Mercedes R. Carnethon[1,5]

Author affiliations:

1. Department of Neurology, Northwestern University Feinberg School of Medicine
2. Department of Preventive Medicine, Northwestern University Feinberg School of Medicine
3. Northwestern University Feinberg School of Medicine
4. SASU Project Management
5. Department of Medicine, Division of Pulmonary and Critical Care, Northwestern University Feinberg School of Medicine

Author Contributions

All authors have contributed to the design of this protocol. AG, DC, FS, KH, KLK, MRC, PZ, SA, and TTV initiated and conceptually designed the project. SC is acquiring data. This protocol was drafted by KH, KLK, MLP, MRC, MW, SC, SJA, and SSR, and was refined for critically important content by DC, SSR, and TTV. Statistical advice was provided by MW and SJA. KLK and MRC obtained funding for the study. All authors approved the final manuscript.

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Patient and public involvement

Patients and/or the public were involved in the design, conduct, and dissemination plans of this research. Refer to the Methods section for further details.

Conflicts of Interest

There are no conflicts of interest to report.

Contact Information:

Kristen L. Knutson, PhD

Associate Professor

Center for Sleep and Circadian Medicine

Department of Neurology

Northwestern University Feinberg School of Medicine

710 N Lakeshore Drive, Room 1003

Chicago, IL 60611

Tel: 312-503-1526

Email: kristen.knutson@northwestern.edu

ORCID: https://orcid.org/0000-0002-2751-6168

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ARTICLE SUMMARY

Abstract

Introduction: Cognitive dysfunction, a leading cause of mortality and morbidity in the US and globally, has been shown to disproportionately affect the socioeconomically disadvantaged and those who identify as Black or Hispanic/Latinx. Poor sleep is strongly associated with the development of vascular and metabolic diseases, which correlate with cognitive dysfunction. Therefore, sleep may contribute to observed disparities in cognitive disorders. The Epidemiologic Study of Disparities in Sleep and Cognition in Older Adults (DISCO) is a longitudinal, observational cohort study that focuses on gathering data to better understand racial/ethnic sleep disparities and illuminate the relationship among sleep, race, and ethnicity and changes in cognitive function. This investigation may help inform targeted interventions to minimize disparities in cognitive health among aging adults.

Methods and analysis: The DISCO study will examine up to 495 individuals aged 55 and older at two time points over 24 months. An equal number of Black, White, and Hispanic/Latinx individuals will be recruited using methods aimed for adults traditionally underrepresented in research. Study procedures at each time point will include cognitive tests, gait speed measurement, wrist actigraphy, a type 2 home polysomnography and a clinical exam. Participants will also complete self-identified assessments and questionnaires on cognitive ability, sleep, medication use, quality of life, sociodemographic characteristics, diet, substance use, and psychological and social health.

Ethics and Dissemination: This study was approved by the Northwestern University Feinberg School of Medicine Institutional Review Board. De-identified datasets will be shared via the BioLINCC repository following the completion of the project. Biospecimen samples from the study that are not being analyzed can be made available to qualified investigators upon review and approval by study investigators. Requests that do not lead to participant burden or that conflict with the primary aims of the study will be reviewed by the study investigators.

Strengths and Limitations

- Strength: Multiple race and ethnic groups are examined in a single study with identical instrumentation and methodology applied across groups.
- Strength: This is a longitudinal follow up study to determine temporality.
- Strength: Gold standard instruments illustrate objective determination of habitual sleep and sleep architecture.
- Limitation: Sample is not generalizable for the population since random sampling is not used.

Keywords

sleep medicine, dementia, epidemiology, health equity, public health

INTRODUCTION AND RATIONALE

Dementia, including Alzheimer's disease, is a severe manifestation of cognitive dysfunction and among the top 10 causes of death in the US and globally.(1) Morbidity from less severe cognitive dysfunction is equally notable, since cognitive dysfunction alone, although not terminal in most cases, still requires progressive social and medical support. The prevalence of cognitive dysfunction is higher among persons with fewer socioeconomic resources, less education, or those who identify as Black or Hispanic/Latinx race and ethnicity.(2) Disparities in the cardiovascular and metabolic correlates of cognitive dysfunction are hypothesized to account for differences in cognitive function by race and ethnicity.(3) However, while these disparities are observed by race and ethnicity, they are likely attributable to differences in socioeconomic resources that provide access to preventive medical care and offer differential access to environmental resources (e.g., healthy foods, safe spaces for physical activity) that promote ideal health. Given the irreversibility of cognitive dysfunction, identifying and addressing these modifiable factors that are associated with cognitive decline could reduce disparities in cognitive dysfunction.(4)

Sleep disturbances are one such potentially modifiable correlate of cognitive dysfunction that vary by race/ethnicity and socioeconomic status.(5-7) Habitual sleep duration and sleep disordered breathing may influence cognition indirectly through the biologically plausible development of cardiovascular and metabolic disorders.(8-12) Alternatively, short sleep duration or sleep disorders may influence cognition dysfunction and dementia via inflammation and endothelial dysfunction.(13, 14)

Non-Hispanic Black and Hispanic/Latinx adults have less favorable patterns of habitual sleep, sleep architecture and sleep disordered breathing as compared with white adults.(15-18) These patterns are observed across the lifecourse, including in epidemiological studies of middle- and older aged adults.(19) Based on prior evidence that sleep characteristics are worse among non-white older adults and the biologically plausible pathways by which poor sleep could influence cognitive functioning, we formed a longitudinal observational epidemiological study to investigate how disparities in sleep among older adults influence cognitive outcomes.

Specific Aims

The primary objectives of the Disparities in Sleep and Cognition (DISCO) study are twofold. The first is to examine numerous social, behavioral, and health-related characteristics as possible explanations for racial and ethnic sleep health disparities. The second is to determine whether disparities in sleep health by race and ethnicity are significant contributors to disparities in the rate of cognitive decline over the course of approximately 2 years.

The study has 2 primary aims:

1. Define the contribution of psychological well-being, social well-being, and clinical characteristics to sleep disparities among older adults.

We will test the hypotheses that sleep disparities by race and ethnicity are partially explained by lower psychological well-being, greater stress, lower self- efficacy, and lower social support among non-White adults; and by a higher burden of prevalent comorbidities, such as heart failure or diabetes among non-White adults.

2. Determine whether sleep disturbances mediate racial or ethnic differences in the change in cognitive function over 24 months.

We hypothesize that inadequate sleep will be associated with greater cognitive decline and will partially mediate the racial and ethnic differences in change in cognitive function over 2 years. We will additionally explore mechanistic pathways to account for these associations, including the presence of cerebral small vessel dysfunction and insulin resistance.

METHODS

Study design

The DISCO study is a longitudinal observational cohort study that will examine 450 older adults with an equal proportion of non-Hispanic Black, non-Hispanic White, and Hispanic/Latinx adults of any race aged 55 years and older. Participants will be examined at baseline and again approximately 24 months later. To account for 10% loss to follow-up, we are enrolling approximately 495 participants at baseline. Women and men will be enrolled at proportions that reflect older age distribution according to the 2019 US Census (54% and 46%, respectively). Study participant enrollment began in July 2019 and will continue through December 2023. Participant follow-up will take place through March 2024.

Study setting

This is a single-site study in the metropolitan Chicago area and surrounding suburbs, and nearby northwest Indiana and southern Wisconsin.

Recruitment methods

Participants are recruited through a combination of strategies including random sampling of commercially available telephone listings, institutional electronic health records, advertisements on social media and in publicly available locations, community engagement strategies, and word of mouth (i.e., snowball sampling).

1. Our recruitment strategy using commercially available sampling and the electronic health record sampling are similar. Our staff mails a letter to potential participants or sends an email to explain the study and invite them to contact study staff to assess eligibility. If potential participants do not attempt to reach us, then our staff call participants to explain the study, invite participation, screen for eligibility, and obtain consent.
2. Advertisements for our study are placed in newspapers, at community sites (e.g., public libraries, cafes, senior living facilities), on public transportation and on Facebook. The advertisements include a link to our study website and staff phone numbers so that individuals can request more information about the study and complete preliminary screening questions to determine their eligibility.
3. Community engagement activities call for the active involvement of community leaders, organizations, and other sectors or stakeholders (such as departments of health) working with academic institutions in the development, implementation, and evaluation of research priorities and activities.(20) The DISCO team engaged with a number of Chicago-area community-based grassroots and health and human services organizations, local and state government

representatives, professional organizations, and other sectors that are not traditionally involved in research. DISCO convenes a Community Advisory Board (CAB) approximately every six-months to provide recommendations on project activities, suggest community engagement opportunities, discuss strategies for recruitment and retention, build relationships with community groups, and inform our team about community events. Most CAB members were identified from organizations that serve Black and Hispanic/Latinx communities in the city of Chicago. While a core group of 3-4 CAB members remain engaged in the study since its inception, the CAB also includes some older adults who enrolled in the DISCO study and joined the CAB after their study participation. When study results are available, the CAB will advise on strategies to disseminate the findings back to the community who contributed to the research.

4. The DISCO staff are also using "snowball sampling," to recruit participants. Staff ask participants who complete the study to refer us to people outside of their household who are socio-demographically similar (based on race, ethnicity, and age) who might also be interested in participating. Study staff ask the participants to share our study flyer and website with these friends and family.

Impact of the COVID-19 Pandemic on Recruitment

The COVID-19 pandemic greatly impacted study recruitment due to the vulnerability of older adults to severe outcomes from SARS-CoV-2.(21) The research clinic was closed from March 16 through June 1, 2020. DISCO pivoted to virtual-only engagement strategies and recruitment activities from March 2020 – June 2022. Following advice from our CAB, we provided virtual educational sessions on relevant topics to increase the community's familiarity with our research team. Additionally, we expanded our digital and print recruitment campaigns and tailored them to our target audience. During this period, we maintained a slower but steady rate of enrollment.

Eligibility criteria

Table 1 summarizes the inclusion and exclusion criteria.

Eligible participants are given the Montreal Cognitive Assessment (MOCA) test either in-person or via the telephone.(22) To administer over the phone (a process that was approved following the pandemic to avoid unnecessary in-person contact), the BLIND MOCA is used, which is a version designed for people with visual impairment. Both versions contain cognitive domains such as attention, concentration, memory, language, conceptual thinking, calculation, and orientation. A pass score on the original MOCA is 26/30, and a pass score on the BLIND MOCA is 18/22. Participants who indicate that their preferred language is Spanish are administered the validated Spanish-language version of the MOCA. If they pass, study staff solicit verbal consent over the telephone and obtain a signed consent using REDCap.

DATA COLLECTION

Examination Structure

Between July 2019 and March 2020, most participants came to the research clinic twice during the baseline examination—first to provide consent, complete questionnaires described in Table 2 and undergo the clinical examination to undergo a fasting blood draw, anthropometric measures, blood pressure assessment, six-minute walk test, NIH Toolbox to assess cognitive function, and to receive the

sleep equipment that they will wear in their homes. On or around the 8th day, participants returned to the research clinic to complete additional cognitive function testing, gait analysis, and measurement of cerebral blood flow (explained below).

From October 2020 going forward, participants are consented to join the study remotely via REDCap and invited to complete the questionnaires prior to the in-person clinical examination. Following receipt of the questionnaires, they attended the clinical examination and to receive the sleep devices (Actiwatch and Sleep Profiler). Participants are provided with the option of returning on the 8th morning or completing the remaining set of cognitive testing elements on that same day. We document the order with which the examination components were captured and devices administered and can account for any variability in our analyses, though we do not anticipate that it will influence our associations.

Participants repeat these examination procedures 6 to 24-months after their baseline assessment.

All data is stored electronically via REDCap and on a secure, encrypted, password-protected server.

Assessment of Cognitive Function

A primary outcome in the study is cognitive function as determined using the *NIH Toolbox cognition battery*.(23, 24) Participants whose preferred language is Spanish are administered the NIH Toolbox Spanish translation. DISCO participants complete the tests that assess attention,(25) executive and memory domains,(26) and episodic memory(27, 28) because of the overlap between Alzheimer's Disease and vascular cognitive impairment (cerebral small vessel disease) in this age group.(29)

A second measure of cognitive abilities is determined using the PROMIS Applied Cognition Abilities Instrument, which is a 16-item measure evaluating self-impressions of cognitive function in the previous seven days in areas such as mental acuity, concentration, and memory.(30)

Sleep Assessment

We are using several methods to assess sleep health in the DISCO study that are consistent with gold-standard measures for in-home unattended assessments in observational population studies.

Wrist Actigraphy

Sleep-wake activity is measured over 7-8 days using wrist activity monitors (Actiwatch Spectrum Plus or Pro ™, Philips Respironics). Wrist actigraphy has been validated against polysomnography (the gold standard of sleep measurements), demonstrating a high correlation for sleep duration among both people with insomnia (r=.82) and in healthy people (r = 0.97) with a discrepancy ranging from 12 to 25 minutes.(31) This method is thought to be a more accurate representation of habitual sleep patterns than polysomnography because it is less disruptive to sleep, can be carried out in the home, and is usually averaged over multiple days. Participants also complete a simple sleep diary and are asked to push the event marker button each time they try to go to sleep and when they wake up.

The actigraphy recordings are scored by a trained technician following specific study guidelines regarding the use of event markers, sleep diary and the activity and light data from the device. We document which method was used to determine the start and end of all rest intervals. All scored recordings are reviewed by PI and Sleep Specialist Dr. Knutson. We use the validated algorithms included in the Actiwatch™ software analysis system (Actiware) to calculate several measures for each

rest interval. The primary actigraphic estimates of habitual sleep include: 1. sleep duration; 2. sleep percentage (%, the sleep period actually spent sleeping; 3. sleep fragmentation (an index of restlessness). We also are calculating rest-activity rhythms and sleep regularity indices using previously published methods.(32, 33)

Type 2 Polysomnography

Attended, in-laboratory, full-polysomnography recordings are the gold standard method to assess sleep architecture (i.e., sleep stages) and respiratory events; however, this method is burdensome on the subject. Thus, we have selected an easy-to-use EEG monitor that can be self-applied and worn at home. We are using the Sleep Profiler™ system (Advanced Brain Monitoring, Carlsbad, CA) to assess sleep stages, spectral power, and respiratory events. The system has configurable acquisition of up to six channels of electro-physiological signals to acquire electroencephalography (EEG), electromyography (EMG), electrooculography (EOG), and electrocardiography (ECG) signals. The device also includes respiratory measures via airflow adapter, cannula, wireless WristOx, Thorax and Abdomen Piezo belts. Several validation studies have been performed comparing the Sleep Profiler to polysomnography and demonstrated strong agreement between these methods.(34, 35) In addition, analysis of two nights of recording demonstrated stability in the measures of the sleep stages, indicating the Sleep Profiler provides valid measures of sleep stages with a single night.(36)

Participants are asked to wear the device for one night and are given detailed instructions and demonstrations, along with both videos and written instructions. The system firmware monitors signal quality to ensure that the sensors are properly applied and that high-quality signals are being acquired. Impedance checking is automatically initiated when acquisition begins. Voice messages are delivered to the patient if the impedances are too high or the sensors have become detached. We disable any voice messaging during sleep, however, because we do not want to impair the sleep of the participants. The acquired signals are saved in a universal data format (European Data Format – EDF) that can be analyzed with third party software, if needed. For our primary analyses, we are using the Sleep Profiler cloud that includes automatic scoring and staging. The pulse rate is analyzed to detect autonomic activation. Head movement is used to assist in detecting sleep/wake and to identify periods with gross movement which result in artifact or indicate behavioral arousals. The software provides visual presentation of the recordings and the ability to rescore by a technician. All recordings are reviewed by a trained technician who modifies the analysis if needed.

The Sleep Profiler System provides the following measures: minutes and percentage of stages of rapid eye movement (REM) sleep, non-REM sleep (N1, N2, N3), sleep latency, wake-after-sleep-onset (WASO), sleep efficiency, arousals, pulse rate, and average power spectra, including delta (or slow-wave activity). The software also detects apneas and hypopneas based on either 3% or 4% desaturation. We are using the American Academy of Sleep Medicine definition of hypopnea when there is a ≥ 3% oxygen desaturation from pre-event baseline and/or the event is associated with an arousal.(37) We then calculate the apnea-hypopnea index (AHI; events/hour).

Sleep Questionnaires

Participants complete several questionnaires to assess subjective sleep quality and chronotype preferences.(38) The following validated instruments are collected at both time points: the Pittsburgh Sleep Quality Index,(39) Insomnia Severity Index,(40) Morningness-Eveningness Questionnaire,(41)

Epworth Sleepiness Scale,(42) and the Brief Index of Sleep Control.(43) See Table 2 for a description of each instrument.

Other Measurements

Cerebral blood flow velocity is assessed via transcranial Doppler (TCD) ultrasound measurements.(44) TCD provides a powerful tool for non-invasive assessment of cerebral vascular responses to various physiological challenges such as motor or cognitive activation or change in blood pressure and end-tidal carbon dioxide, which we know are regulated at the level of arterioles or resistance vessels of the brain (cerebral small vessels). After 10 minutes of resting data is recorded, participants perform cognitive tasks and then perform the cerebral vasoreactivity test, which is assessed using the CO2 breathing and hyperventilation method. The resting data is used to calculate cerebral autoregulation and pulsatility index, the cognitive trial will be used to calculate neurovascular coupling and the breathing trial will be used to measure vasoreactivity. These cognitive tests are completed only at baseline for all but a small proportion of participants (<5%).

Table 2 lists the remaining domains that are assessed in the study. We selected these domains with the goal of capturing the multidimensional factors that could influence sleep or cognitive function. We assessed a broad set of social determinants of health that we know underlie disparities in health behaviors and disease outcomes by race and ethnicity. All questionnaires that did not have Spanish language translations available were translated by our study team or professional translation company and reviewed by two additional Spanish-speaking co-investigators.

Sociodemographic characteristics including race, ethnicity, age, and educational level were determined based on self-report from the participants. Wherever possible, validated questionnaires were used to assess covariates that we hypothesized were associated with sleep, cognitive function, or both.

Participants are also asked to walk across a 25-ft mat (ZenoMat, Protokinetics, PA) and their walking speed is measured during two trials in order to measure gait speed, which has been strongly associated with blood pressure, cardiovascular disease and stroke.(45-48)

DATA MANAGEMENT

Sample size and power calculation

Analyses in both aims will include the entire proposed sample of 495 recruited participants. Power to detect clinically meaningful effect sizes were calculated conservatively assuming 9% (n=450) and 18% (n=405) of participants would have missing data for primary analyses or would be lost to attrition. A study that examined sleep quality, including percentage of wake after sleep onset (WASO),(49) found that sleep after days with lower subjective stress had a lower percentage of WASO than sleep after days with higher stress (mean WASO% = 12.2% vs. 16.4%, SD = 12.1% vs. 14.9%). We have 91% power to detect these differences with the proposed sample of 450 participants and 87% power to detect this difference assuming 10% attrition (n=405) in Aim 1 analyses. For power analyses using the Structural Equation Modeling (SEM) approach in Aim 2, we calculate the power to detect both unacceptable model-fit using Root Mean Square Error of Approximation (RMSEA) and effect sizes. With a sample size of n=450, we achieve 92% power to detect an RMSEA of 0.1 (unacceptable model fit) against the null hypothesis of RMSEA = 0.5 (good model fit). With a sample size of n=450 participants and using RMSEA = 0.05 under the null hypothesis of a good model fit and RMSEA = 0.1 under the alternative hypothesis of

unacceptable model fit, we can achieve a power of 92% by observing 5 variables of interest. Assuming 10% are lost to follow-up after baseline, with the sample size of n=405 we can achieve a power of 89%.(50) With the proposed sample size, we can achieve an effect size of 0.2 (small-moderate effect size) with 5 observed variables and 5 latent variables.(51, 52) Furthermore, with n=405, we achieve 87% power to detect an odds ratio of 3:1 in cognitive decline for the group with adequate sleep compared to the group with inadequate sleep.

The definition of "inadequate sleep" will vary based on the hypotheses under study. We are capturing a comprehensive set of measures of sleep health including habitual sleep as well as sleep architecture. We plan to examine multiple dimensions of sleep health, including sleep duration and wake after sleep onset (WASO), but in secondary analyses we can explore the wealth other measurements that we collected and develop a composite "sleep health" score as has been proposed in the literature. We have the flexibility to generate composite sleep health scores so that we can produce research that is aligned with contemporary research objectives.

Quality Control and Quality Assurance

Study data are collected using electronic methods that constrain response ranges to plausible ranges. Participants either enter responses directly into the REDCap system or data are entered by study staff members who interviewed study participants. The analytical team meets monthly to review data regarding data completeness, data quality and additional data topics as needed. This process will ensure proper data management, scoring of questionnaires and completion of study procedures in a timely manner.

Data analysis plan

General considerations: In all analyses, distributional characteristics of each measure and residual diagnostics will be used to assess modeling assumptions. As needed, transformations, nonparametric methods, and/or inclusion of higher-order (quadratic, cubic, interaction, etc.) terms may be considered in analytic models. Statistical estimates (e.g., regression coefficients) will be reported with accompanying 95% confidence intervals and p-values as applicable. We will use type I error rate of 0.05 to assess statistical significance, while also qualitatively determining if the effect magnitude is clinically meaningful.

Missing data: The multilevel models planned for analysis of longitudinal data are generally robust for unbalanced data across study time points. Nonetheless, multiple imputation with chained equations will then be used to examine the sensitivity of findings to missing data.(53) For non-ignorable missing data, we will conduct sensitivity analyses using non-ignorable pattern-mixture and selection models to investigate the robustness of our conclusions across the different models for missing data.

Analyses for Aim 1. To evaluate the contribution of psychosocial characteristics to sleep disparities, we will compare the coefficient estimate for race in models including versus excluding each characteristic of interest. The base model for the primary analyses will be a linear regression model with WASO duration as the outcome and race, sex, and age as explanatory variables. Each subsequent model will add a psychosocial characteristic (e.g., depressive symptoms) to the base model and calculate the percentage reduction in the estimated coefficient for race in the expanded model compared to the base model. This same modeling strategy will be used to evaluate the contribution of characteristics to disparities in self-

reported sleep quality (e.g., PSQI) or sleep disorders. Secondary analyses will examine the cross-sectional associations between measured psychosocial variables and objective and subjective measures of sleep. We will fit regularized regression models (e.g., LASSO, elastic net) for each sleep outcome (e.g., WASO, PSQI) that include interaction terms between race and psychosocial characteristics to assess effect modification by race.(54) These models will be adjusted for sociodemographic characteristics and comorbidities measured at the baseline visit. The final models will identify the psychosocial variables that best explain each sleep outcome. Additional analyses will stratify by OSA (i.e., AHI < or >= 15) and by sex. OSA is not an exclusion.

Analyses for Aim 2. We will assess whether WASO is associated with greater cognitive decline over 24 months via mixed-effects models for change in continuously determined cognitive function score, with a random intercept for participant to account for the correlation that arises from measuring multiple time points from an individual.(55) The mixed-effects models will be adjusted for time-invariant (e.g., sex) and time-varying (e.g., body mass index, comorbid disease) covariates. Results from this analysis will inform whether baseline sleep measurements or change in sleep measurements will be used in subsequent analyses. To assess whether WASO mediates racial/ethnic differences in change in cognitive function over 24 months, we will use two approaches to mediation analysis: the Baron and Kenny mediation method and Vanderweele's causal mediation method, which allows for interactions between the independent and mediator variable.(56-58) Furthermore, we will test for interactions between the sleep variables and race/ethnicity to determine if different aspects of sleep vary by race. We will use the same analytic approach to test to what extent cerebral vascular blood flow or insulin resistance mediate the association between WASO and other sleep metrics and cognitive function.

ETHICS and DISSEMINATION

The DISCO study is approved by the Northwestern University Feinberg School of Medicine Institutional Review Board (IRB). As stated above, informed consent is obtained in writing from participants and stored in Study Tracker. All data will be de-identified before sharing the results, posing no risk to participant confidentiality.

De-identified datasets will be shared via the BioLINCC repository following the completion of the study. In addition to the ongoing processing of biospecimens during the study, study investigators are banking serum, plasma and buffy coat. Samples that are not being analyzed can be made available to qualified investigators with a materials transfer agreement and/or data use agreement as applicable. The study investigators will review and consider all requests that do not lead to participant burden nor conflict with the primary aims of the study.

Table 1. Inclusion and exclusion criteria

Inclusion	Exclusion
At least 55 years of age at the time of enrollment	Currently undergoing treatment for cancer (other than non-melanoma skin cancer)
Non-Hispanic Black, non-Hispanic White, or Hispanic/Latinx of any race	Clinical vascular event including myocardial infarction, stroke, transient ischemic attack, or procedure to treat those conditions within the previous 6 months
Able to read and understand either English or Spanish	Chronic heart failure classes II-IV
	Diagnosis of dementia (including Alzheimer's disease)
	Living in a group home, assisted living or other institution
	Overnight shift work or swing shift work that spans midnight (12:00am)
	Severe vision or hearing deficits that would interfere with testing
	Regular use of medications in the following classes: hypnotics, psychoactive medications with anti-cholinergic and antihistaminic effects, or opioids
	Severe chronic obstructive pulmonary disease
	Inability to move both arms
	Prior diagnosis of severe neurological disorders
	Montreal cognitive assessment (MOCA) score < 23 if administered the in-person version, or <18 if administered the over-the-phone version
	Inability to give consent

Table 2. List of survey instruments used in this study

Instrument	Description
Cognitive Domain	
MOCA(59)	Assessment tool for the early detection of mild cognitive impairment. Assesses short-term memory, visuospatial abilities, executive function, attention, concentration and working memory, language and orientation to time and place.

PROMIS Applied Cognition Abilities(28)	16-item measure assessing self-impressions of cognitive function in the past 7 days.
Sleep Domain	
Pittsburgh Sleep Quality Index(39)	19-item instrument to estimate subjective sleep quality. Scores range from 0 to 21; higher scores indicate worse sleep quality.
Insomnia Severity Index(40)	7-item instrument that assesses severity of insomnia. Higher scores indicate worse insomnia symptoms.
Morningness-Eveningness(41)	19-item instrument that assesses preferred “chronotype”, or morningness vs eveningness. Higher scores indicate greater morningness.
Epworth Sleepiness Scale(42)	8-item questionnaire to estimate daytime sleepiness. Higher scores indicate greater sleepiness.
Brief Index of Sleep Control(43)	4-item instrument designed to quantify the degree to which someone has control over their sleep. Higher scores indicate greater control.
Health Domain	
Medication Use	This form collects details on prescription medication used in the past 4 weeks or over-the-counter medication used in the past 2 weeks.
Medical History	23-item questionnaire that records information about individuals' medical history. High scores indicate better health.
SF-36 Questionnaire(60)	36-item measure assessing health-related quality of life. Scores are summarized in a Physical Component Summary (PCS) and Mental Component Summary (MCS). Higher scores indicate better health status.
KC Cardiomyopathy Questionnaire(61)	23-Item measure examining heart failure symptoms, physical limitations and quality of life. Lower scores represent more severe symptoms/limitations.
PROMIS Global Health(62)	10-item scale that assesses physical, mental, and social aspects of health. Higher scores indicate better health.
Time Use Questionnaire	7-item scale that assesses the frequency and duration of activities.
COVID-19 Questionnaire	15-item questionnaire that related to exposure to COVID-19.
Sociodemographic Domain	
Sociodemographic Information Questionnaire	38 items are collected to assess sociodemographic characteristics such as age, gender, ethnicity, education level, income, access to healthcare, perceived social standing etc.
Lifestyle Behavior Domain	
GPAQ(63)	13-item scale examining several components of physical activity including intensity, duration and frequency.
Tobacco History	11- item questionnaire that determines when an individual began smoking and their current smoking habits.
ASA 24-Hour Dietary Recall(64)	Automated self-administered 24-hour dietary assessment tool web-based tool.
Substance Use	12-item questionnaire that determines the use of alcohol and marijuana.
Psychosocial Domain	

STRAIN(65)	The Stress and Adversity Inventory (STRAIN) is a secure, online stress assessment system that measures individuals' lifetime exposure to different types of acute and chronic stress that can affect mental and physical health. The system is intended to combine the reliability and sophistication of an interview-based measure of stress with the simplicity of a self-report instrument. To accomplish this goal, the STRAIN enquires about 75 different types of stressors (Adolescent STRAIN) or 55 different types of stressors (Adult STRAIN) that cover all major life domains (e.g., health, intimate relationships, friendships, children, education, work, finances, housing, living conditions, crime, etc.) and several social-psychological characteristics (e.g., interpersonal loss, physical danger, role change, entrapment, etc.).
PROMIS Social Isolation - Short Form 4a(66)	6-item scale examining perceived social isolation. Higher scores indicate higher perceived isolation.
Quick Inventory of Depressive Symptomatology QIDS-SR16(67)	16-item scale examining endorsement of depressive symptoms. Higher scores indicate higher symptoms.
Perceived Stress Scale(68)	10-item scale assessing the degree to which situation in participant's life are appraised as stressful. Higher scores indicate higher levels of stress.
UCLA Loneliness Questionnaire(69)	8-item scale assessing perceived isolation from others. Higher scores indicate higher perceived loneliness.
GAD Anxiety(70)	7-item questionnaire assessing self-reported anxiety symptoms in the past two weeks. Higher scores indicate higher anxiety symptoms.
Brief Resilience Scale(71)	6-item questionnaire used to assess the ability to bounce back. High score indicated high resilience,
Bereavement	1-item examining whether participants have lost a spouse/partner or loved one in the past 6-months.
USDA Food insecurity(72)	5- item questionnaire used to measure household food security and food insecurity. High score indicated extremely low food security.
Social Support(73)	8- item questionnaire indicated the number of people available for support and satisfaction of support.

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Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

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Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a

Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	n/a
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1-2
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	1
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support			
Sources	#5a	Indicate sources of financial or other support for the review	1
Sponsor	#5b	Provide name for the review funder and / or sponsor	1
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	1
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is	4

		already known	
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	12
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	5
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Study records - data collection	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any	10

process		processes for obtaining and confirming data from investigators	
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	10
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	10
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within	3

		studies)	
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	10